

Original Article

Iodine nutrition status and thyroid function of women at different phases of gestation in an iodine sufficient rural area

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Background and Objectives: This study was undertaken to evaluate the status of iodine nutrition and thyroid function of women at different phases of gestation in an iodine sufficient rural area. **Methods and Study Design:** 215 pregnant women in different trimesters were consecutively enrolled in iodine sufficient rural areas of Yongjing county of Gansu province, China. The blood samples and random urine samples were collected from them, and serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb) and urinary iodine were measured. **Results:** Median Urinary Iodine (MUI) of three groups of pregnant women (first, second and third trimester) were 190 µg/L, 153 µg/L and 145 µg/L respectively. With the increase of gestational age, the level of FT3 decreased. And the FT3 level in the first trimester was higher than those in the second and third trimester. There was a U-shaped curve seen between the TSH levels and the gestational age. The medians of TgAb and TPOAb appeared the lowest in the first trimester. Significant difference was seen in TgAb and TPOAb levels of the three groups of pregnant women. The incidence of thyroid function disorder was 1.86%, including subclinical hypothyroidism accounted for 1.40% and hypothyroidism accounted for 0.47%. The incidence of thyroid function disorder mainly appeared in the early pregnancy. Abnormal FT3, TSH, positive TgAb and TPOAb were mainly seen during early pregnancy. **Conclusions:** The levels of serum TSH and thyroid hormones fluctuate at the different phases of pregnancy. With the increase of gestational age, the incidence of iodine deficiency also increased. Abnormal thyroid hormones, TSH, positive TgAb and TPOAb were mainly existed in the early pregnancy.

Key Words: pregnant women, iodine status, thyroid hormones, urinary iodine

INTRODUCTION

Pregnancy is a special physiological process. In this period, iodine nutrition not only affects the thyroid function of pregnant women and the fetus itself, but also further affects the fetal brain development and offspring intelligence. Since 1990, due to the implementation of the universal salt iodization (USI) policy worldwide, serious iodine deficiency diseases have been nearly eradicated, and some countries or regions implementing the USI have even appeared excessive iodine.¹ Nevertheless, for some vulnerable groups of iodine deficiency, such as pregnant women, there are still different degrees of iodine intake deficiency. Schoolchildren are the conventional group for assessing community iodine nutrition. But adequate iodine intake in schoolchildren does not ensure that pregnant women in the same community are iodine sufficient, because urine iodine in schoolchildren is not a good indicator to reflect iodine nutrition of pregnant women. In some developing countries and high-income countries including the UK and the U.S, many pregnant women do not get enough iodine.^{2,3} An effective iodized salt program has brought iodine sufficiency to most of general population of China, but pregnant women in some areas

may still risk deficiency and need further supplements.⁴⁻⁶ The problem even exists in those countries that have sufficient iodine supplies for several decades.^{7,8} One study in China show that during first trimester, both mild iodine deficiency and excessive iodine intake had adverse impacts on pregnancy outcomes in an iodine-sufficient area, China.⁹ So the iodine nutrition and thyroid function of pregnant women have received widespread attention in the world.^{10,11} The objective of this present study was to assess the iodine nutritional status and thyroid function of pregnant woman and their relationship in rural areas with adequate iodine intake, provide theoretical basis and guidance for pregnant woman to carry out the relevant

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monitoring and scientific iodine intake and reduce or eliminate the adverse effects of abnormal iodine intake, improve the quality of the population.

METHODS

Yongjing county of Gansu province, China was selected as study site where coverage rate of iodized salt and edible rate of qualified iodized salt are both >95% and urinary iodine medians of schoolchildren are around 200 $\mu\text{g/L}$ for many years. Yongjin County was divided into five geographic locations (east, south, west, north and center). In each location, one rural community was identified and fifteen samples of each group were selected randomly (three groups of first, second and third trimester pregnant women) (Figure 1). Recruitment criteria included women aged 19-40 years who had lived in the county for more than 10 years and were pregnant. Women with a history of thyroid disease or other chronic diseases were excluded and subjects on any medical regimen before pregnancy that may affect thyroid function, such as glucocorticoids, dopamine, or antiepileptic drugs were also excluded. A total of 215 pregnant women met the inclusion criteria of this study, including 70 pregnant women in first trimester, 72 pregnant women in second trimester and 73 pregnant women in third trimester.

Samples of spot urine and blood were obtained from each participant in the morning after all-night fasting. Serum TSH, FT4, FT3, TPOAb, TgAb and urinary iodine were measured. Casual urine samples were refrigerated at 4°C until laboratory analysis. Iodine in urine was measured by the National standard method of China's Ministry of Health, based on the catalytic effect of iodine on the reaction between cerium IV and arsenic III, adapted from the general Sandell-Kolthoff technique recommended by ICCIDD.¹² External reference samples were provided by the National Laboratory for Prevention and Treatment of Iodine Deficient Disorders in China. The determination standard is the recommended standard for monitoring pregnant women made by WHO,¹³ on basis of which, urine iodine median less than 150 $\mu\text{g/L}$ is an insufficient iodine intake; 150-249 $\mu\text{g/L}$ urine iodine median is an appropriate intake; 250-499 $\mu\text{g/L}$ urine iodine median is an intake which is more than appropriate amount of iodine intake; urine iodine median ≥ 500 $\mu\text{g/L}$ is an exces-

sive intake. Iodized salt was determined by GB/T13025.7-2012 direct titration method.¹⁴

Serum was prepared by centrifugation within 2h of blood collection and frozen at -20°C until analysis of thyroid hormones. TSH, FT4, FT3, TgAb and TPOAb were measured by chemiluminescent immunoassay (CLIA) with Roche E-601 electrochemiluminescence detector, Switzerland. Reference value of pregnant woman refers to normal adult value of detection hospital: TSH 0.7-10.0 $\mu\text{IU/mL}$, FT3 3.19-9.15 pmol/L; FT4 9.11-25.47 pmol/L; The reference of TPOAb 0-40 IU/mL, and TgAb 0-70IU/mL were provided by the manufacturer. The criterion of thyroid dysfunction was defined as: Overt hypothyroidism, TSH \uparrow , T4 \downarrow , T3 \downarrow ; subclinical hypothyroidism, TSH \uparrow , with normal FT4; isolated hypothyroxinemia, FT4 \downarrow , with normal TSH, negative TPOAb and negative TgAb; Hyperthyroidism, TSH \downarrow and FT4 \uparrow . The positive TPOAb was >40 IU/mL and a positive TgAb was >70 IU/mL.

Before the study, women groups were explained about the study and consents were obtained. The study protocol was approved by ethical committee of Gansu Center for Diseases Control and Prevention and conducted in accordance with the Declaration of Helsinki.

Statistical Analysis: Data processing and analysis were performed using SPSS (version 13.0, SPSS Inc, Chicago, IL, USA). The urine iodine, TgAb and TPOAb are expressed by median, comparison between groups used non parametric test; TSH, FT4, FT3 are expressed by mean, groups were compared using analysis of variance; rate comparison is tested by Chi square test.

RESULTS

Urine iodine level in different pregnancy

The urinary iodine medians of three groups of pregnant women (first, second and third trimester) were 190 $\mu\text{g/L}$, 153 $\mu\text{g/L}$ and 145 $\mu\text{g/L}$ respectively. With the exception of pregnant women in the third trimester, the urinary iodine medians of pregnant women in the first and second trimesters were in the 150-249 $\mu\text{g/L}$ range defined as optimal by WHO/UNICEF/ICCIDD. There was significant difference in urinary iodine median among three groups of pregnant women ($\chi^2=7.12$, $p=0.028$) and with the prolongation of pregnancy, urine iodine decreased

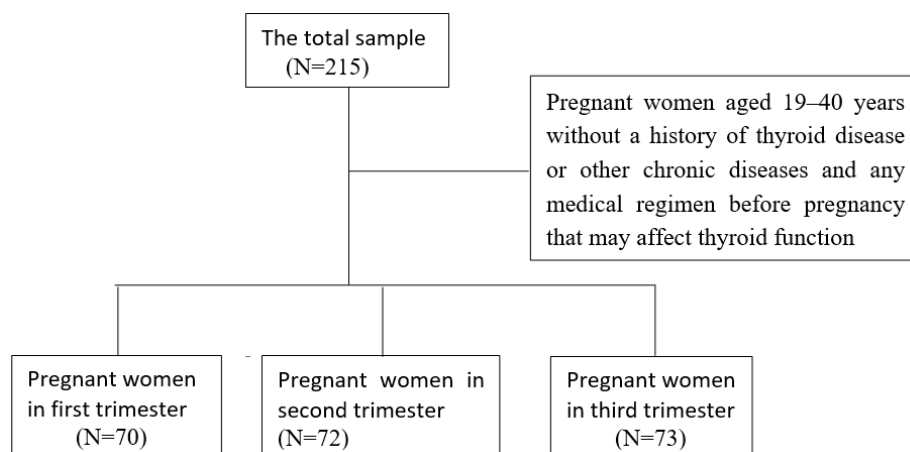


Figure 1. Flow chart the sample selection.

Table 1. Urinary iodine for pregnant women in different pregnancy groups

Trimester of pregnancy	No	Median (µg/L)	Frequency distribution (% (N))			
			0-	150-	250-	500-
First	70	190	35.7 (25)	37.1 (26)	20.0 (14)	7.1 (5)
Second	73	153	47.9 (35)	38.4 (28)	12.3 (9)	1.4 (1)
Third	72	145	52.8 (38)	23.6 (17)	8.3 (6)	15.3 (11)
All	215	156	45.1 (97)	33.5 (72)	13.5 (29)	7.9 (17)

Table 2. FT3, FT4 and TSH in different pregnancy groups

Trimester of pregnancy	FT3		FT4		TSH	
	Mean±SD (min-max)	Abnormal (% (N))	Mean±SD (min-max)	Abnormal (%(N))	Mean±SD (min-max)	Abnormal (% (N))
First	6.55±2.60 (1.00-16.50)	5.71% (4)	16.65±3.62 (10.80-24.30)	0 (0)	4.92±3.84 (1.60-28.10)	3 (4.29%)
Second	5.75±1.81 (3.00-9.10)	1.37% (1)	17.26±3.89 (10.50-24.60)	0 (0)	2.41±1.43 (1.00-8.60)	0 (0)
Third	5.30±1.55 (3.20-8.90)	0 (0)	16.96±3.75 (10.30-24.90)	1.39% (1)	3.30±1.97 (1.10-8.30)	1.39% (1)
All	5.86±2.08 (1.00-16.50)	2.33% (5)	16.96±3.75 (10.30-24.90)	0.47% (1)	3.53±2.80 (1.00-28.10)	1.86% (4)
F/p	F=6.98, p=0.001		F=0.47, p=0.622		F=16.86, p=0.000	

gradually. See Table 1.

Level changes in thyroid hormone and thyroid stimulating hormone in different pregnancy

With the increase of gestational age, the level of FT3 decreased ($p<0.05$), the FT3 level in the first trimester was higher than those in the second and third trimester ($p<0.05$). There was no significant difference in FT3 level among the second trimester and third trimester ($p>0.05$). There were five cases with abnormal FT3, including four cases in first trimester and one case in the second trimester. There was no significant difference in FT4 during pregnancy, $p>0.05$. Only 1 case in third trimester had abnormal FT4. There was significant difference in TSH values among the three groups of pregnant women ($p<0.01$), with a U-shaped curve seen between TSH levels and gestational age. The first trimester had the highest TSH level and the second trimester had the lowest TSH level. Abnormal TSH was in 4 cases, including 3 cases in first pregnancy (4.29%), 1 case (1.39%) in third pregnancy, see Table 2.

Thyroid autoantibodies in different pregnancy groups

The lowest median of TgAb (12.1 IU/mL) is in first trimester pregnancy. The highest median of TgAb (18.1 IU/mL) is in second trimester pregnancy. There was statistically significant difference of TgAb during different pregnancy, $p<0.01$; TgAb in first trimester pregnancy was significantly lower than that in third pregnancy ($Z=-2.69$, $p=0.007$). There were total 6 cases (2.79%) with positive TgAb, including 4 cases (5.71%) in first trimester pregnancy, 1 case in the second and 1 case in third trimesters respectively. The lowest median of TPOAb (7.16 IU/mL) is in first pregnancy. There was statistically significant differences of TPOAb in different trimester pregnancy ($p<0.01$). TPOAb in first trimester pregnancy was significantly lower than those in second and third trimester pregnancy ($Z=-2.56$, $p=0.011$ and $Z=-2.92$, $p=0.003$). There were 2 cases (0.93%) with positive TPOAb, and 1

case each in the first and second trimester, respectively. See Table 3.

Prevalence of thyroid dysfunction in different pregnancy groups

Thyroid dysfunction incidence was 1.86% in different pregnancy. The subclinical hypothyroidism accounted for 1.40%, hypothyroidism accounted for 0.47%, which mainly distributed in the early stages of pregnancy. See Table 4.

DISCUSSION

Iodine is an important substance for the production of the thyroid hormones, T4 and T3, which are vital for normal growth and development particularly of the brain and central nervous system. In order for pregnant women to produce enough thyroid hormones to meet both her own and her baby's requirements, a 50% increase in iodine intake is recommended.¹⁵ Iodine nutrition during pregnancy can affect the maternal thyroid function, which in turn can have adverse effects on the mother and the fetus.¹⁶ Pregnant women are in special physiological processes. Normal pregnancy entails substantial changes in maternal thyroid function. In adequate adaptation to these changes in thyroid physiology results in thyroid dysfunction.^{17,18} Insufficient iodine intake can lead to miscarriage, fetal growth retardation and neonatal hypothyroidism,¹⁹ excessive intake can cause subclinical hypothyroidism, hypothyroxinemia,²⁰ causing miscarriage, premature birth and other adverse pregnancy outcomes, which has serious impact on maternal and fetal health. Increasing attention has therefore focused on the diagnosis and treatment of maternal thyroid dysfunction during pregnancy.

Optimal iodine nutritional status during pregnancy is essential for maintaining both proper thyroid function in mothers and normal development of the brain of progeny during fetal and early post-natal life. As neonatal thyroid function has not been established in the early trimester of pregnancy, so the growth and development of the fetus mainly rely on maternal thyroid hormones. Because iodine is essential for the synthesis of thyroid hormones,

Table 3. Thyroid antibody in different pregnancy groups

Trimester of pregnancy	TgAb		TPOAb	
	M (min-max)	Positivity (% (N))	M (min-max)	Positivity (% (N))
First	12.10 (3.00-95.60)	5.71% (4)	7.60 (2.40-70.50)	1.43% (1)
Second	18.10 (1.10-93.00)	1.37% (1)	10.50 (1.90-44.20)	1.37% (1)
Third	17.50 (5.70-84.20)	1.39% (1)	10.35 (2.00-37.30)	0 (0)
χ^2/p	$\chi^2=10.11$ $p=0.006$		$\chi^2=12.59$ $p=0.002$	

Table 4. Various types of thyroid dysfunction in different pregnancy groups

Trimester of pregnancy	N	Normal (% (N))	Low FT4 (% (N))	Subclinical hypothyroidism (% (N))	Hypothyroidism (% (N))	Subclinical hyperthyroidism (% (N))	Hyperthyroidism (% (N))
First	70	91.4% (64)	0 (0)	2.86% (2)	1.43% (1)	0 (0)	0 (0)
Second	73	98.6% (72)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Third	72	98.6% (71)	0 (0)	1.39% (1)	0 (0)	0 (0)	0 (0)
Total	215	96.3% (207)	0 (0)	1.40% (3)	0.47% (1)	0 (0)	0 (0)

iodine deficiency in the mother may lead to insufficient thyroid hormone synthesis in mothers and fetus, resulting in the impairment of the neuropsychological development in infants.^{21,22}

According to the WHO/UNICEF/ICCIDD recommended criteria for pregnant women, a median urinary iodine concentration (UIC) of 150–249 $\mu\text{g/L}$ indicates an adequate iodine intake.²³ In the present study, the total urinary iodine median of pregnant women was 156 $\mu\text{g/L}$, which has just reached the WHO/UNICEF/ICCIDD-recommended criteria for pregnant women. Urinary iodine median of pregnant women in the first, second, third trimester were 190 $\mu\text{g/L}$, 153 $\mu\text{g/L}$ and 145 $\mu\text{g/L}$ respectively. With the increase of gestational age, urinary iodine level of pregnant women showed a downward trend, and in the third trimester, the median urinary iodine has been lower than the standard recommended by WHO and the difference of median urine iodine in three group pregnancy was statistically significant ($p<0.05$).

The indicator of UIC should not be used for the purposes of individual diagnosis and treatment. As an indicator of iodine intake, median UIC does not provide direct information about thyroid function.²³ In individual pregnant woman, the best surrogate for measuring iodine sufficiency is maternal thyroid function.²⁴

Maternal thyroid hormone synthesis and metabolism had a series of physiological changes, including increase of thyroxine binding globulin, human chorionic promote gonadal hormone levels, placental type III deiodinase activity and kidney clearance rate, etc. These physiological changes affected the level of thyroid hormones in the body, resulting in change of thyroid hormone levels during pregnancy. Therefore, understanding iodine nutrition of women at different phases of gestation and the thyroid function and changing rules of it is very important for maintaining the health of pregnant women and their fetuses. The present study showed with the increase of gestational age, the level of FT3 decreased ($p<0.05$), the FT3 level in the first trimester was higher than those in the second and third trimester ($p<0.05$). The difference of FT3 level has no statistical significance in the second trimester and third trimester. Abnormal FT3 mainly distributed in the early stages of pregnancy (4 cases (5.71%)). There was no significant difference in FT4 level between different gestation periods. TSH level was the highest in the early pregnancy, the lowest in the second

trimester, and rose again in the third trimester, but lower than that in the early trimester, presenting a u-shaped curve. There was statistically significant difference in TSH level in different pregnancies. FT3 and TSH abnormalities were mainly in early pregnancy. The incidence of thyroid dysfunction was 1.86%, in which subclinical hypothyroidism accounted for 1.40% and hypothyroidism accounted for 0.47%, also mainly in the early pregnancy. Thyroid autoantibody is a marker of thyroid autoimmune, and the positive rate in hashimoto's thyroiditis patients is almost 100%, followed by a higher positive rate in relatives of patients with graves' disease or autoimmune thyroid disease.²⁵ The median TGAb and TPOAb levels in early pregnancy were the lowest, while the levels in middle and late pregnancy remained at a high level. The differences in antibody levels in different pregnancies were statistically significant ($p<0.01$). A total of 6 cases (2.79%) were TGAb positive, among which 4 cases (5.71%) were early pregnancy. A total of 2 cases (0.93%) were TPOAb positive, with 1 case in the first trimester and 1 case in the second trimester. Studies have confirmed that the decrease of thyroid autoantibody level in pregnant women in the first trimester may be related to the increase of inhibitory T cells, the decrease of helper T cells, and the increase of lymphocyte suppressors such as of A-2 macroglobulin and the significant increase of cortisol hormone level in pregnant women.²⁶ Domestic and foreign studies have confirmed that maternal thyroid hormone deficiency during pregnancy causes irreversible damage to fetal brain development.²⁷

Early pregnancy is the rapid development period of the fetal brain, fetal thyroid function at this time have not yet been established. The thyroid hormone needed for brain development mainly from the mother, so this maternal thyroid hormone deficiency will cause irreversible damage on fetal brain development. This investigation found that FT3, TSH abnormalities and TGAb and TPOAb antibody positivity were mainly distributed in the early pregnancy, suggesting that it is important to carry out thyroid function related detection in the early pregnancy. In addition, with the increase of gestational age, the urine iodine level presents a downward trend, and the deficiency of iodine nutrition in pregnant women is intensified. Although the thyroid gland of the fetus in the third trimester can synthesize thyroid hormone, the iodine comes from the mother, so it is necessary to carry out monitoring of

iodine nutrition during pregnancy to ensure adequate pregnancy iodine nutrition.

Despite the adequate supplementation of iodine intake, some pregnant women appear not to be protected against iodine deficiency. Programs as monitoring urinary iodine as well as screening thyroid function targeting all the pregnant women should be carried out.

AUTHOR DISCLOSURES

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